

A STUDY ON SERUM URIC ACID LEVELS IN ESSENTIAL HYPERTENSION AND ITS RELATION WITH SEVERITY, DURATION OF HYPERTENSION, SERUM CHOLESTEROL AND TRIGLYCERIDE LEVELS

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ABSTRACT

Back Ground & Objective

The topical role of uric acid and its relation to cardiovascular disease, renal disease, and hypertension is rapidly evolving. The association of raised serum uric acid levels with various cardiovascular risk factors has often led to the debate of whether raised serum uric acid levels could be an independent risk factor in essential hypertension. Hence we carried out a study to see if there is a relationship between serum uric acid and hypertension and its correlation with lipid cholesterol and triglycerides.

Methodology

The study was carried out in M B S Hospital, & Associated Group of Hospitals, Medical College, Kota, Rajasthan. The study period was from January 2012 to November 2012. A total of 100 patients were studied of which 50 were cases and 50 controls. The patients were included if they satisfied the JNC VII criteria for hypertension. They were excluded if they were having any other condition known to cause raised serum uric acid levels & secondary hypertension.

Results

The study showed that serum uric acid levels were raised in patients with hypertension in comparison to normotensives. Uric acid showed a rise in stage 2 of hypertension and duration > 5 years. There were high levels of cholesterol and triglycerides in patients with hyperuricemia.

Interpretation & Conclusions

We concluded that measuring uric acid is a useful test for the clinician, as it carries important prognostic information.

KEYWORDS: Serum Uric Acid, Hypertension, JNC VII, Hyperuricemia, eNO, Redox Shuttle

INTRODUCTION

Raised serum uric acid has been reported to be associated with an increased risk of coronary heart disease and is commonly encountered with essential hypertension, even untreated hypertension, and type II diabetes, which are in turn associated with coronary heart disease. It is not known whether raised serum uric acid increases the risk of hypertension and type II diabetes independently of known risk factors such as age, obesity, alcohol consumption, and physical activity ¹.

The topical role of uric acid and its relation to cardiovascular disease, renal disease, and hypertension is rapidly evolving. Hypertension is strongly associated with hyperuricemia. SUA levels are elevated in hypertension and are present in 25% of untreated hypertensive subjects, 50% of subjects taking diuretics, and greater than 75% of patients with malignant hypertension ².

Uric acid is a marker of risk and it remains controversial as to its importance as a risk factor (causative role). The role of uric acid, oxidative – redox stress, reactive oxygen species, and decreased endothelial nitric oxide and endothelial dysfunction cannot be over emphasized. In the atherosclerotic prooxidative environmental milieu the original antioxidant properties of uric acid paradoxically becomes prooxidant, thus contributing to the oxidation of lipoproteins within atherosclerotic plaques³.

Hence we carried out a study to see if there is a relationship between serum uric acid and hypertension and its correlation with triglycerides and cholesterol.

METHODOLOGY

Study Population

The study was carried out in M B S & Attached group of Hospitals. The study period was from January 2012 to November 2012. A total of 100 patients of age group 30 – 60 years were studied of which 50 were cases and 50 controls. The patients were included if they satisfied the JNC VII criteria for hypertension. They were excluded if they were having any other condition known to cause raised serum uric acid levels & secondary hypertension.

After informed consent, brief clinical history and examination was done to rule out renal disorders, liver disorders or any other condition that would affect the parameters under study. We excluded patients with Diabetes Mellitus II, rheumatoid arthritis, renal disorders, C.O.P.D., gout, liver diseases. Blood Pressure was measured in reclining position.

Sample Collection

After overnight fasting, samples were collected in the morning. The samples were left standing for one hour and then serum was separated by centrifugation at 3000 rpm for 10 minutes. The samples were analyzed on the same day on EM 360 fully auto analyzer (Transasia) in Central Lab, MBS Hospital.

Lipid Profile Tests

Serum total cholesterol was estimated by enzymatic CHOD-POD method.

Triglycerides were estimated using CHOD-POD method.

Uric acid was measured using Uricase method.

Statistical Analysis

Statistical analysis was carried out on Microsoft excel. Continuous parameters were expressed as mean \pm SD. Student's t test was applied to the data. The Pearson correlation was used to correlate uric acid with triglycerides & cholesterol levels. P value < 0.05 was considered statistically significant.

RESULTS

During the 11 month study period from January 2013 to November 2013 a total of 100 patients were studied of which 50 patients were cases that were categorized into Stage 1 or Stage 2 hypertension (base on JNC VII classification) and 50 were controls who were patients without hypertension or any other condition known to cause raised serum uric acid levels.

The total number of male cases was 30 and the total no of female cases 20. The age group ranged from 30 years to 60 years.

The total number of male controls was 30 and the total no of female controls were 20. The age group ranged from 30 years to 60 years. The controls were adjusted with the cases for age and sex, shown in Table 1 and Table 2.

Table 1: Age Distribution for Cases and Controls

AGE in Years	CASES		CONTR OLS	
	N0.	%	No.	%
31 - 40	6	12	6	12
41 - 50	18	36	18	36
51-60	26	52	26	52
Total	50	100	50	100

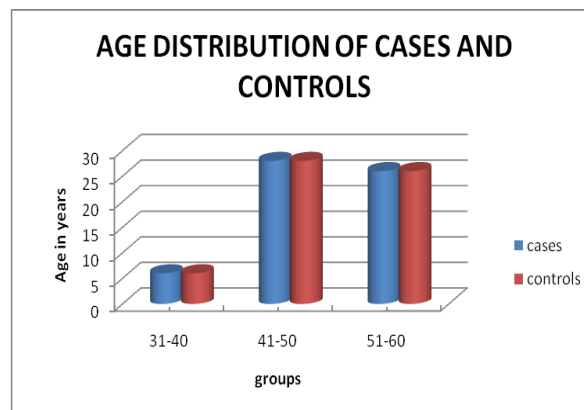


Figure 1

Table 2: Sex Distribution of Cases and Control

CATEGORY	CASES	CONTROLS
MALE	30	30
FEMALE	20	20

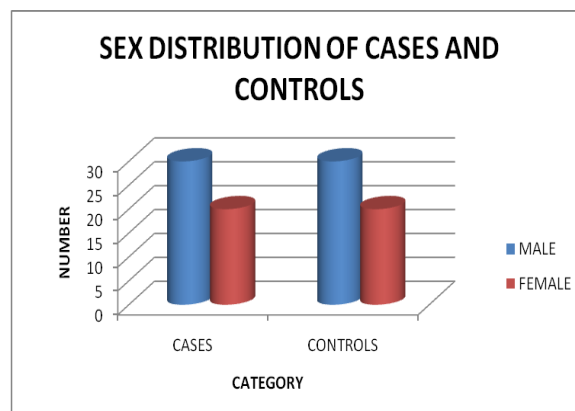


Figure 2

SUA and Risk between Cases and Controls

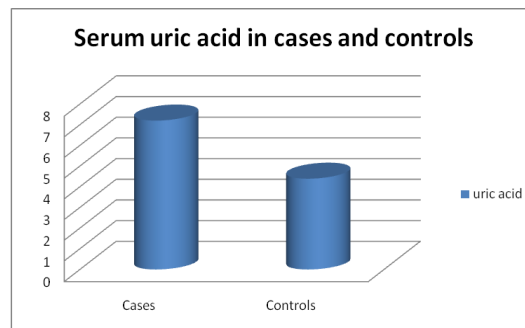
The total number of cases were 50 (both male and female), the data analysis of the cases showed the mean SUA level to be 6.938 with a standard deviation of 1.143 (6.938 ± 1.143).

The total number of controls of controls were 50 (both male and female), the data analyzed showed a mean SUA level of 4.39 with a standard deviation of 0.87 (4.39 ± 0.87), as shown in table 3

Table 3: SUA Level between Cases and Controls

SUA Levels between Cases and Controls Category	Number	Mean \pm SD
Cases	50	6.938 \pm 1.143
Controls	50	4.39 \pm 0.93

t= - 12.356 and p <0.0001 which is extremely statistically significant.

**Figure 3**

SUA and Risk for Severity of Hypertension

The severity of hypertension was divided into stage 1 and stage 2 based on the JNC VII classification of hypertension. In the study done at our hospital the total number of patients assessed to have stage 1 hypertension was 14 patients (both male and female patients), the total number of patients having stage 2 hypertension was 36 (both male and female patients).

The data analysis for SUA levels in the stages of hypertension showed a mean serum uric acid level in stage 1 hypertension of 6.385 with a standard deviation of 1.235.

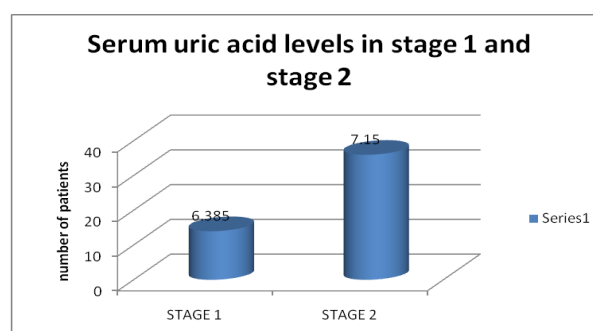
In stage 2 of hypertension of 7.15 with a standard deviation of 1.04.

The t-value was - 2.067 and a p-value of .04 which was significant. The data analyzed showed that there was a significant rise in hypertension in patients who were having stage 2 hypertension i.e. those with a SBP \geq 160 and a DBP \geq 100 than those with stage 1 hypertension (SBP 140- 159 and DBP 90 - 99)

Table 4

Stage of Hypertension	Number of Patients	Mean \pm SD
Stage 1	14	6.385 \pm 1.235
Stage 2	36	7.15 \pm 1.04

t= - 2.067 p=0.0440 statistically significant.

**Figure 4**

SUA Levels Based on Duration of Hypertension

The duration of hypertension was divided into 2 categories - those with hypertension for duration of hypertension < 5 years and those with duration of hypertension ≥ 5 years.

The total number of patients with hypertension for duration of < 5 years was 18, and the total number of patients with duration of hypertension ≥ 5 years was 32. The mean SUA level in patients with hypertension < 5 years was 5.988 with a standard deviation of 1.216.

The mean SUA level in patients with hypertension ≥ 5 years was 7.471 with a standard deviation of 0.67.

The analyzed data showed a t-value of - 4.7647 and a p-value < .0001 which showed that there is significant increase in SUA levels in patients with hypertension ≥ 5 years than those with a duration of < 5 years.

Table 5

Duration of Hypertension	Number of Patients	Serum Uric Acid Mean \pm SD
< 5 years	18	5.988 \pm 1.216
≥ 5 years	32	7.471 \pm 0.67

t= - 4.7647 p<0.0001

Study Parameters of Cases and Controls

Levels of triglycerides were 127 mg/dl with a standard deviation of 48.24 in controls and 232.98 mg/dl in cases with a standard deviation of 67.86 in cases.

Levels of cholesterol were 173.74 mg/dl with a standard deviation of 42.44 in controls and 250.18 with a standard deviation of 56.49 in cases.

Table 6

Study Parameters	Controls	Cases	t= Value	p= Value	Significance
TG	127 \pm 48.24	232 \pm 67.86	- 8.949	<0.0001	Extremely statistically significant.
Cho	173.74 \pm 42.44	250 \pm 56.49	-7.649	<.0001	Extremely statistically significant.
Uric acid	4.39 \pm 0.93	6.938 \pm 1.143	-12.356	<0.0001	Extremely statistically significant.

Results are presented in Mean \pm SD.

Cases have high levels of serum triglycerides, cholesterol and uric acid with p value < 0.001 which is extremely statistically significant.

Pearson Correlation of serum uric acid with serum cholesterol and triglycerides

Table 7

Pair	Controls		Cases	
	R Value	P Value	R Value	P Value
UA vs TG	0.065	0.653	0.105	0.468
UA vs CHO	0.200	0.164	0.112	0.439

The relationship between uric acid and lipid parameters is distorted in cases when compared to controls.

Scatter Diagram Showing Correlation between Uric Acid and Triglycerides in Cases and Controls

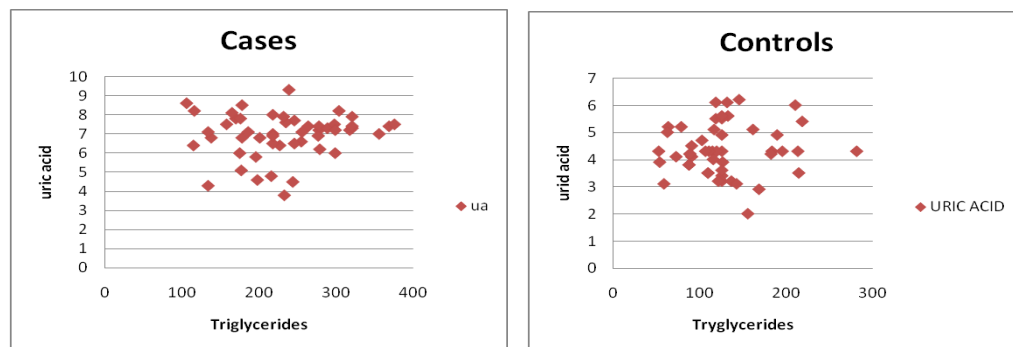


Figure 5

Cases with high triglycerides have hyperuricemia

Controls have normal triglycerides and uric acid.

Scatter Diagram Showing Correlation between Uric Acid and Cholesterol in Cases and Controls

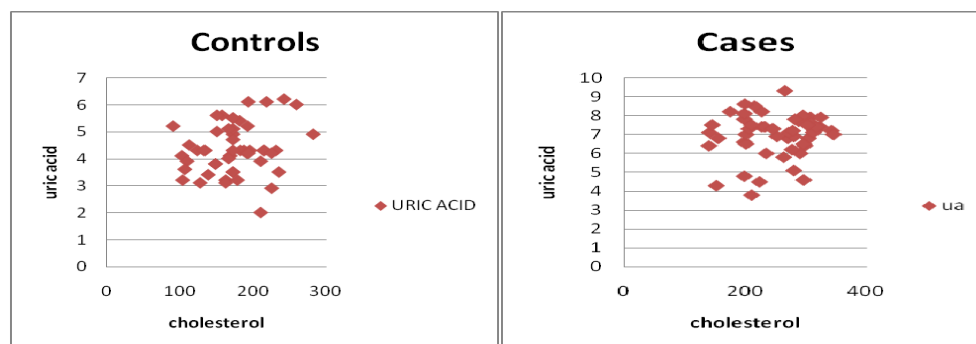


Figure 6

Controls have normal cholesterol and uric acid

Cases have high cholesterol and uric acid

DISCUSSIONS

The study shows that patients with hypertension have high serum uric acid levels. Uric acid is raised in stage 2 of hypertension as compared to stage 1. Hypertension more than 5 years also causes increase in uric acid levels as compared to less than 5 years. Patients with hypertension had high levels of cholesterol and triglycerides as compared to controls.

According to Mehmet Kanliay, Mark Segal et al uric acid is biologically active and can stimulate oxidative stress, endothelial dysfunction, inflammation and vasoconstriction. Epidemiologically studies have found uric acid can independently predict the development of hypertension, stroke and heart failure. Experimentally raising uric acid in animals increase Blood Pressure and lowering uric acid can reduce Blood Pressure⁴.

According to a prospective study of 83,683 Australian men serum uric acid is independently related to morbidity from CHF and stroke⁵.

Elevations of uric acid > 4 mg/dl should be considered a "red flag" in those patients at risk for cardiovascular disease and should alert the clinician to strive to utilize a global risk reduction program in a team effort to reduce the

complications of the atherogenic process resulting in the morbid – mortal outcomes. Johnson RJ *et al.* have nicely demonstrated that hyperuricemia predicts cardiovascular events in the general population, the hypertensive population, and patients with pre-existing CVD. Furthermore hyperuricemia predicts the development of future hypertension⁶.

Potential mechanisms involved with the association of hyperuricemia and hypertension include the following³:

- Decreased renal blood flow (decreased GFR) stimulating urate reabsorption
- Microvascular (capillary) disease resulting in local tissue ischemia.
- Ischemia with associated increased lactate production that blocks urate secretion in the proximal tubule and increased uric acid synthesis due to increased RNA-DNA breakdown and increased purine (adenine and guanine) metabolism, which increases uric acid and ROS through the effect of xanthine oxidase (XO).
- Ischemia induces increased XO production and increased SUA and ROS. These associations with ischemia and XO induction may help to understand why hyperuricemia is associated with preeclampsia and congestive heart failure.

Because endothelial dysfunction, local oxidant generation, elevated circulating cytokines, and a proinflammatory state are common in patients with cardiovascular disease and hypertension there is an increased level of oxidative – redox stress within vascular tissues. Oxidative – redox stress results in impaired endothelium-dependent vasodilation with quenching of endothelial nitric oxide (eNO) and allows the endothelium to become a net producer of ROS specifically superoxide as the endothelial nitric oxide synthase (eNOS) enzyme uncouples to produce superoxide instead of eNO.^{6,7}

An Antioxidant – Prooxidant Urate Redox Shuttle

Antioxidants may become prooxidants in certain situations¹¹⁻¹⁵. Therefore the existence of an antioxidant – prooxidant redox shuttle in the vascular milieu of the atherosclerotic macrovessel intima and the local sub endothelial capillary interstitium of the microvessel is suggested^{10,11,12}.

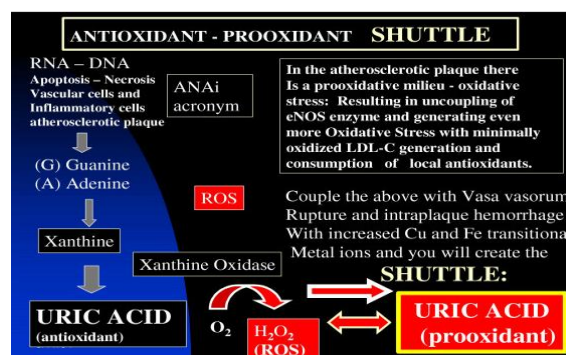


Figure 7

Antioxidant – Prooxidant Urate Redox Shuttle

The antioxidant – prooxidant urate redox shuttle is an important concept to understand regarding accelerated atherosclerosis. This shuttle is important in understanding the role of how the antioxidant uric acid becomes prooxidant in this environmental milieu, which results in its damaging role to the endothelium and arterial vessel wall remodeling with an elevated tension of oxidative – redox stress (ROS), accelerated atherosclerosis and arterial vessel wall remodeling³.

SUA in the early stages of the atherosclerotic process is known to act as an antioxidant and may be one of the strongest determinates of plasma antioxidative capacity¹³.

However, later in the atherosclerotic process when SUA levels are known to be elevated (in the upper 1/3 of the normal range >4 mg/dl and outside of the normal range >6 mg/dl in females and 6.5–7 mg/dl in males) this previously antioxidant (SUA) paradoxically becomes prooxidant. This antioxidant – prooxidant urate redox shuttle seems to rely heavily on its surrounding environment such as timing (early or late in the disease process), location of the tissue and substrate, acidity (acidic – basic – or neutral pH), the surrounding oxidant milieu, depletion of other local antioxidants, the supply and duration of oxidant substrate and its oxidant enzyme. In the accelerated atherosclerotic – vulnerable plaque the intima has been shown to be acidic¹⁴, depleted of local antioxidants with an underlying increase in oxidant stress and ROS and associated with uncoupling of the eNOS enzyme and a decrease in the locally produced naturally occurring antioxidant: eNO and endothelial dysfunction^{7,11,12}.

The upper 1/3 of the normal physiologic – homeostatic range (> 4 mg/dl) and abnormal elevations (> 6.5 or 7 mg/dl in men and > 6.0 mg/dl in women) in SUA definitely should be considered as one of the multiple injurious stimuli to the arterial vessel wall and capillary, which may contribute to endothelial dysfunction and arterial – capillary vessel wall remodeling through oxidative – redox stress^{7,8,9}.

It possible that SUA levels could be as similarly predictive as hsCRP since it is a sensitive marker for underlying inflammation and remodeling within the arterial vessel wall and the myocardium¹⁷.

Uric acid is known to induce the nuclear transcription factor (NF-kappaB) and monocyte chemoattractant protein-1 (MCP-1)¹⁸. Regarding TNF alpha it has been shown that SUA levels significantly correlate with TNF alpha concentrations in congestive heart failure and as a result Olexa P *et al.* conclude that SUA may reflect the severity of systolic dysfunction and the activation of an inflammatory reaction in patients with congestive heart failure¹⁹. Additionally, uric acid also stimulates human mononuclear cells to produce interleukin-1 beta, IL-6, and TNF alpha⁶.

From a clinical standpoint, hyperuricemia should alert the clinician to an overall increased risk of cardiovascular disease and especially those patients with an increased risk of cardiovascular events. Hyperuricemia should therefore be a "red flag" to the clinician to utilize a team effort in achieving an overall approach to obtain a global risk reduction program

Measuring uric acid is a useful test for the clinician, as it carries important prognostic information. An elevation of uric acid is associated with an increased risk for cardiovascular disease and mortality³.

CONCLUSIONS

With the results based on the study carried out we concluded that there can be a direct relation between hyperuricemia and hypertension. Also the study showed that the SUA levels were significantly increased in patients with Stage 2 hypertension in comparison with those with stage 1 hypertension. The study also showed that the duration of hypertension had a significant impact on the SUA levels, those with a longer duration of hypertension had significantly raised SUA levels when compared with those of a lesser duration. We also saw raised levels of cholesterol and triglycerides in patients with hyperuricemia. Finally we concluded that measuring uric acid is a useful test for the clinician, as it carries important prognostic information. An elevation of uric acid is associated with an increased risk for cardiovascular disease and mortality. It can be used as an early biochemical marker to determine the severity and duration of hypertension.

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